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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/662,128	09/14/2000	Shuji Miyagawa	197330US0	9580

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/29/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/662,128	MIYAGAWA ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,3 and 5-35* is/are pending in the application.

4a) Of the above claim(s) *12-24,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3,5-11 and 30-33* is/are rejected.

7)☒ Claim(s) *25-33* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 2, 3, 5-35 are pending in the application.

This Office Action is in response to the Amendment filed on 11/15/02.

Claims 1 and 4 are cancelled. Claims 12-24, 34 and 35 are withdrawn from consideration for being directed to non-elected subject matter. Claims 2, 3, 5-11 and 25-33 are currently under examination.

Election/Restrictions

Claims 34 and 35 are withdrawn from consideration for being directed to non-elected subject matter. Applicants elected inventions of Group I in paper no.13, which is drawn to a modified Cre recombinase gene. Claims 34 and 35 are drawn to a method of knock-in and knock-out a gene, which belongs to the inventions of Groups II and III respectively.

Response to Amendment

The rejection of claim 8 under 35 U.S.C.101 has been withdrawn in light of Applicants' amendment of the claim.

The rejection of claim 8 under 35 U.S.C.112 1st paragraph has been withdrawn in light of Applicants' amendment of the claim.

Claims 5-11 and newly added claims 30-33 are rejected under 35 U.S.C.112 2nd paragraph for reasons set forth of the record mailed on 7/15/02.

Claims 2, 3, 7-11 are rejected under 35 U.S.C.103(a) for reasons set forth of the record mailed on 7/15/02 and further discussed below.

Claims 25-33 are objected to for being dependent on a rejected claim.

Response to Arguments

Rejection under 35 U.S.C.112 2nd paragraph

In response to the rejection of claims 5 and 6, Applicants argue that the terms "location specific promoter" and "time specific promoter" are supported by the specification on page 9. Applicants further cited Mohan et al. and Fahlen et al. to demonstrate that these terms are commonly used in the art.

These arguments have been considered but are deemed not persuasive. The specification only discloses that the promoter can be induced by a substance location specifically and time specifically. The specification neither explains what does these terms encompass nor gives examples of these inducible promoters that are time or location specific. The first sentence of the abstract in Mohan article talks about time and location specific expression of genes within the context of embryonic development. Fahlen et al. describes location specific regulation of transgenic Ly49A receptor by MHC class I molecules, however, does not teach any location specific promoter. Therefore, neither of these articles provide support for these terms. As such, the metes and bounds of the terms cannot be established. This rejection is maintained.

Applicants fail to respond to the rejection of claims 8-11 under 112 2nd paragraph. Therefore, this rejection is maintained for same reason as discussed in the previous office action (see page 6).

Newly added claims 30-33 are rejected for the same reason as applied to claim 8-11.

Rejection under 35 U.S.C.103(a)

Claims 2, 3, 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over St-Onge et al (1996, Nucleic Acid Research, Vol 24, No. 19, 3875-3877) and Bergemann et al.

(1995, Nucleic Acid Research, Vol 23, No. 21, 4451-4456), in view of Zhang et al (1996, Biochemical and Biophysical Research Communications, Vol 227, 707-711) and Nakamura et al (1998, Nucleic Acid Research, Vol 26, No. 1, 334).

In response to the rejection, Applicants argue that the combination teaching of the references does not provide reasonable expectation of success for increased expression of the modified Cre recombinase. Applicants argue that the success of the change in codons in the jellyfish GFP provided by Zhang reference is more evolutionary related to mammals than bacteria so that there is no expectation of success of making similar changes in bacterial protein and achieve the same effect. Applicants further argue that the high expression of the Cre in CHO cells is a result of modified Cre recombinase couple to the inducible promoter.

These arguments have been considered but deemed not persuasive. Nakamura et al. teach the optimal codon usage for a number of organism encompassing mammals to virus. Based on this information, there is reasonable expectation of success to optimize protein expression in these systems. In addition, Zhang et al. already demonstrated such success. Changing a bacterial codon to mammalian codon does not make it different than changing a jellyfish codon to mammalian codon because the optimal codon for mammalian expression is known.

Applicants assert that the high expression of the Cre in CHO cells is a result of modified Cre recombinase couple to the inducible promoter because the vector comprising the modified Cre with the inducible promoter results in substantially same recombination efficiency relative to constitutive promoter, while the vector comprising the wild type Cre with inducible promoter results in decreased expression. Applicants conclude that the combination of the references cited

in the previous office action does not teach this aspect. Contrary to Applicants' assertion, the combination of the references have taught a Cre recombinase with a inducible promoter (see teachings of St-Onge et al of the previous action). This Cre recombinase would have an increased expression if the codons are modified for optimal expression in mammalian system. Based on the teaching of Zhang et al. and Nakamura et al., there is reasonable expectation of success to modify the bacterial codon to mammalian codon and achieve higher expression in mammalian cells. Therefore, claims 2, 3, 5 and 7 stand rejected because the invention was obvious to one of ordinary skill of art when the invention was made.

Claims 8-11 are drawn to a non-human animal, an organ, a tissue or a cell into which the polynucleotide encoding a modified Cre is introduced.

The teaching of St-Onge et al., Nakamura et al. and Zhang et al. was discussed in the previous office action.

It would have been obvious to one of ordinary skill of art to make a non-human mammal, an organ, a tissue or a cell expressing the modified Cre recombinase because of the combination teaching of St-Onge et al., Nakamura et al. and Zhang et al. St-Onge et al. teach a transgenic mouse comprising a Cre recombinase gene under the control of CMV promoter fused to seven copies of tetO sequences (see page 3875, 1st column, lines 7-9). The cell, tissue, organ of this transgenic mouse all expressing Cre recombinase. One of ordinary skill in the art would have been motivated to modify the coding sequence of this wild type Cre in this mouse to those of optimized for mammalian cells to increase the expression of the Cre such as the example demonstrated by Zhang et al. The ordinary skill in the art would have reasonable expectation of success because of the teaching of Nakamura et al., which provide the optimized codon for a

variety of organisms. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill of art at the time the invention was made.

Claims 25-33 are objected to for being dependent on a rejected claim.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
January 27, 2003

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER